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Case Report

Low Insulin-like growth factor I (IG–I) level underlying recurrent infection in congenital cystic adenomatoid malformation (CCAM) and MyelodysplasticSyndrome with Chromosome 5q Deletion

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Abstract

Background : Insulin-like growth factor I (IGF-I) is a polypeptide hormone produced mainly by the liver in response to the endocrine GH stimulus, but it is also secreted by multiple tissues for autocrine/paracrine purposes. IGF-I is partly responsible for systemic GH activities although it possesses a wide number of own properties (anabolic, antioxidant, anti-inflammatory and cytoprotective actions). IGF-I is a closely regulated hormone. Low IGF-1 level are observed in GH deficiency or GH resistence. If acquired in childhood, these condition result short stature. Currently the best characterized conditions of IGF-I deficiency are Laron Syndrome, in children; liver cirrhosis, in adults; aging including age-related-cardiovascular and neurological diseases; and more recently, intrauterine growth restriction. Most GH resistence in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness. The purpose of this case report is to summarize the decreasing list of roles of IGF-I underlying pathological desease.

Case : The patients were hospitalized with short stature weight 18 kg, height 118 cm (under –3SD), The patient suffering chronic infection sience 2 years old with repeatly bronchiectasis infection. She has n't had menarche and episode Of hypoglycemia until nowand result examination Trigliseride : 95 mg/dl (normal : 30-150), Hemoglobin 8,1 g/dl, WBC 5,3 thousand/µl, Platelet 109 thousand/µl, Glucose 80 mg/dl, HDL: 21 mg/dl, LDL : 45 mg/dl, TSHs : 2,0 µIUmol/l, FT4: 12.16 þmol/l, Estradiol : < 11.80 pg/ml , FSH : 0.54 mlU/ml, LH : < 0.07 mlU/ml GH : 4.63 ng/ml, IGF-1 : < 25 ng/ml, Cranium scan no found tumor hypothalamic and pituitary, Bone marrow examination supports the diagnosis of MDS with multilineage dysplasia , MSCT of the thorax showed suspect cystic bronchiectasis, would be a Congenital Cystic AdenomatoidMalformation.and cytogenetic analized showed Chromosome number of single cell : 46, There were 20 cell been analized and 8 of cell were been counted Kariotipe : 46,XX,del 5q31.

Conclusion : Low IGF-1 level in this patient due to severe systemic illness (recurrent infection of congenital cysticadenomatoid malformation (CCAM) and deletion 5qMyelodisplatia syndrome (MDS)and poor nutrition.

Keywords : IGF-1 (Insulin-like growth factor I), congenital cystic adenomatoid, malformation (CCAM),Myelodisplatia syndrome (MDS)

BACKGROUND

Insulin-like growth factor 1 (IGF-1) is a 70-amino acid polypeptide (molecular weight 7.6 kDa). IGF-1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF-1 is produced by many tissues, but the liver is the main source of circulating IGF-1. IGF-1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF-1 is transported by IGF-binding proteins, in particular insulin-like growth factor binding protein 3 (IGFBP-3). [1]

IGF-1 is produced when growth hormone (GH) is produsedin pituitary gland and secreted into the blood stream. The presence of growth hormone in the blood initiates the production of IGF-1 in the liver. The role of IGF-1 is to produce growth in the cells of the body.[2] Low IGF-1 level are observed in GH deficiency or GH resistence. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for malignancies. Most GHresistence in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness.[1]

Congenital cystic adenomatoid malformation (CCAM) is a rare entity and is considered as a focal pulmonary dysplasia. It is defined as a multicystic mass of a pulmonary tissue in which there is proliferation of immature bronchial structures at the expense of alveolar

development. This lesion occurs more often in males with a ratio of 1.8:1, and is primarily unilateral, but may occur bilaterally . Associated anomalies are rare. Bronchogenic cysts arise from abnormal budding of the tracheobroncheal tree during airway development. Although bronchogenic cysts are more often present in mediastinum , approximately one third are located in the lung parenchyma, usually within the lower lobes. These cysts contain air, fluids or both. Clinical manifestation are related to various mass efects or secondary infection of the cyst. Pulmonary sequestration is defined as a lung tissue mass that receives its blood supply from an anomaous systemic artery and does not communicate with the bronchial tree via an antomically normal bronchus. Some CCAM lesions present only at birth with respiratory distress symptoms but are confirmed by an abnormal chest radiograph or computed tomography scan. Most CCAMs present with respiratory distress or compromise during infancy or recurrent pneumonias in later years, including adulthood. Typically, chest radiography reveals multiple air filled thin- walled cysts of varying sizes.[2]

Van Den Berghe established 5q- syndrome as a discrete clinical entity in 1974 when he described patients with macrocytic anaemia, thrombocytosis, dyserythropoiesis, hypolobulated megakaryocytes and an interstitial deletion within chromosome 5q. With del(5q) as the sole cytogenetic abnormality, 5q- syndrome. The search for a minimal common deleted region (CDR) on the long arm of 5q has spanned at least 30 years and relied on physical methods of mapping chromosomerepresents an opportunity to define precisely the molecular defect(s) underlying the pathogenesis of this disease.

The finding of a sole karyotypic abnormality in 5q- syndrome in the presence of such a clear 'genotypephenotype' relationship has offered a unique opportunity to explore the precise genetic defect(s) underlying the pathogenesis of this disease entity. 5q. Various groups have analysed chromosome 5q deletions in patients with 5q- syndrome and patients with del(5q) abnormalities with other chromosomal aberrations.[3]

CASE REPORT

Medical history

A 16 years old women with short stature : weight 18 kg, height 118 cm (under –3SD), BMI 12.9 kg/m^2. She was born of an uncomplicated full term pregnancy and normal delivery. At 2 years old, she was diagnosed tuberculosis and treated for 2 years. After complication of developed on end off. She usually had poor appetite. From the 7 years old ,she looked shorter and smaller compared with her friends. She has n'thad menarche and episode Of hypoglycemia until now.

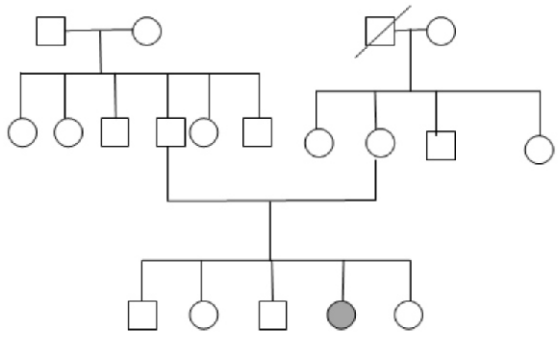

Figure 1. Pedigree of the first family with the patient IGF-1 deficiency.

TABEL 1
Laboratory finding

Test	Result
Hemoglobin (g/dl)	8.1
WBC (thousand/ul)	5.3
Platelet (thousand/ul)	109
Glucose (mg/dl)	80
SGOT (U/l)	51
SGPT (U/l)	45
Alkali Fosfatase (U/l)	436
Gamma GT (U/l)	270
Total Bilirubin (mg/dl)	0.27
Direct Bilirubin (mg/dl)	0.17
Total Protein (g/dl)	7.5
Albumin (g/dl)	2.5
TSHs (µIUmol/l)	2.0
FT4(þmol/l)	12.16
Trigliseride (mg/dl)	95
LDL(mg/dl)	45
Estradiol(pg/ml)	< 11.8
FSH(mIU/ml)	0.54
LH(mIU/ml)	< 0.07
GH(ng/ml)	4.63
IGF-1(ng/ml)	< 25

Gynecologic ultrasound

Obtained ovaries and uterus are normally. Impression supports the diagnosis of MDS with multilineage dysplasia.

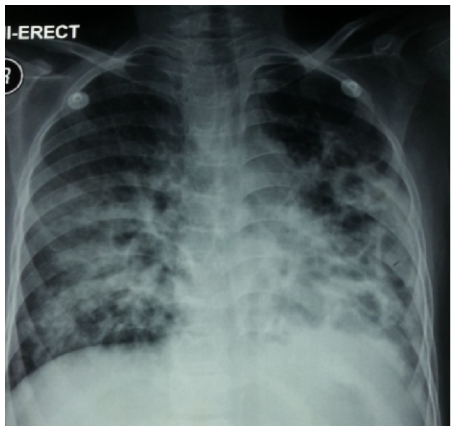

Figure 2. Thorax photo examination. Preview bronkhiectasis. Suspect right effusion pleural.

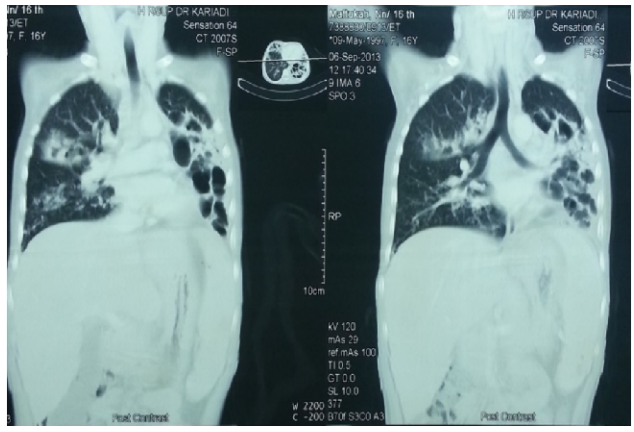

Figure 3. MSCT of the thorax showed suspect cystic bronchiectasis, would be a Congenital Cystic Adenomatoid Malformation. IQ : below average

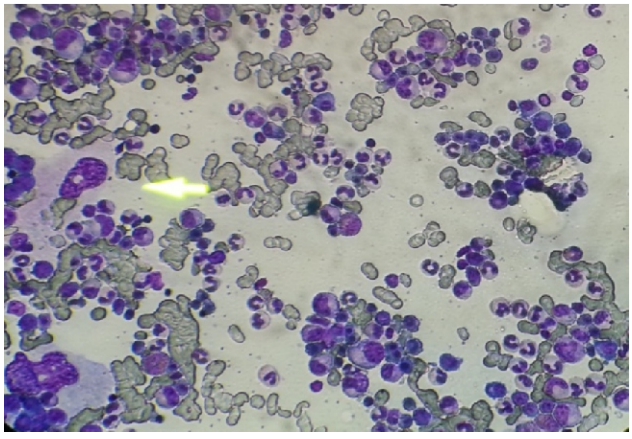

Figure 4. Bone marrow examination

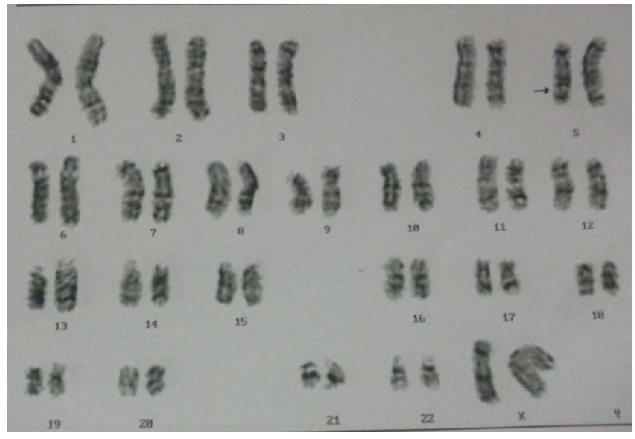

Figure 5. Cytogenetic result. Chromosome number of single cell : 46. There were 20 cell been analized and 8 of cell were been counted. Kariotipe : 46,XX,del 5q31

Bone survey X photo

Impression: Invisible abnormalities in skeletal survey x photo .Epiphyseal growth plates did not closed.

DISCUSSION

Growth disorder in this patient would be caused severe systemic illness1 and chronic malnutrition. Chronic malnutrition caused injury of liver so IGF–1 to be deficiency. IGF–1 deficiency has also been called growth hormone insensitivity syndrome or growth hormone resistency syndrome. IGF-1 deficiency was first described in a severe form, due to a block of growth hormone action at the level of the growth hormone receptor. As a consequence of this abnormal growth hormone receptor function, little IGF–1 is produced. However , patients with severe IGF–1 deficiency have normal concentration of growth hormone (measureable in the blood). This primary form of severe IGF–1 deficiency is differentiated from secondary forms of IGF–1 deficiency or growth hormone insensitivity, caused by, for example, malnutrition or liver desease.[1] This syndrome of GH resistance (insensitivity) was named by Elders *et al* as Laron dwarfism, a name subsequently changed to Laron Syndrome (LS). Molecular studies revealed that the causes of GH resistance are deletionsor mutations in the GH receptor gene, resulting in the failure to generate IGF–1 and a reduction in the synthesis of several other substances, including IGFBP-3.[2]

The hair pubic and breasts patient did not grew normally , and the patient had not been menstruating (Tanner's stage 1).[3] The involvement of the IGF–1 system as intraovarian regulators of folliculogenesis has been intensively studied in a variety of mammal species, and it is now established that ovary is a site of IGF–1 gene expression and reception.[2] IGF–1 may play a role at different stages of follicular development :a) Initiation of growth of the primordial follicle;b) At a secondary follicle stage, IGF–1 may be involved on induction of FSH-R expression on granulose cell and their differentiation,

Figure 6. The patient compared with her brother age 21 old.

theca cell survival and cortical granules formation in oocytes. 2c) at antral follicular stage, IGF–1 may increase follicle sensitivity to gonadotropin, oocyte maturation and LH-R expression in granulose.[2] Laron syndrome is a hereditary disease where there is a primary resistance to growth hormone because of a polymorphic molecular defect in the growth hormone receptor. It is clinically and in many biochemical aspects undistinguishable from isolated growth hormone deficiency (IGHD), and is characterised by high circulating growth hormone concentrations and low serum IGF–I values, which do not rise upon exogenous growth hormone administration. This disease, also called Laron type dwarfism, was first described in Israel in 1966. One of the characteristic laboratory findings is the highcirculating plasma concentrations of growth hormone.[2] Concomitantly there are low or undetectable serum concentrations of IGF-I.Growth hormone receptor is encoded by a single gene located on the short arm of chromosome 5 (5p13–p12). Laronsyndrome is due to a variety of homozygous point mutations in the growth hormone receptor gene10:4 in this patient deleted gene located on the long arm of chromosome 5 (5q31) not 5p13-12. So unlikely this patient a Laron syndrome.

Severe systemic illness in this patient caused bronchiectasis with recurrent infection sience childhood (Congenital CysticAdenomatoid Malformation/CCOM) and myelodisplatia syndrome (MDS). The classical histological change of CCAM is that normal pulmonary alveoli are replaced by cysts composed of adenomatoid hyperplastic bronchioles. Based on the size and number of the cysts, this lesion was initially classified into 3 groups. All types are intrinsically the same lesion, but vary on the radiological presentation. Type I CCAM accounts for 70% of cases, is characterized by single ormultiple cysts more than 3 cm in diameter lined by pseudostratified ciliated columnar epithelium, along withmucous cells which are considered to potentially mutant to adenocarcinoma . Type II lesion is consisted of multiple terminal bronchiolar–like uniform cysts smaller than 2 cm in diameter, lined by cuboidal to columnar epithelium. Type III CCAM usually involves an entire lobe of lung and has a spongy-like appearance, constructed by bulk gland-like structures.[4]

Most CCAM in adults involve unilateral lobes of the lung, and may be complicated with pulmonary bacterial infections and abscesses. Late-onsetCCAM in adults may be more complicated on radiographicimages due to recurrent infections. By far, bacterial infectionis the most frequently reported CCAM complicationwhich causes acute fever and lung abscess.[5,6]

Approximately 15% of patients with MDS have abnormalities of chromosome 5. These abnormalities include interstitialdeletion of a segment of the long arm of chromosome5q [del(5q), 5q–syndrome], monosomy, and unbalancedtranslocations. 5q–syndrome as MDS category was definedby theWorld Health Organization (WHO)[7] and it is characterizedby refractory macrocytic anemia with dyserythropoiesis, transfusion dependence, normal to elevated plateletcounts, hypolobated and nonlobated megakaryocytes,female preponderance, a favourable prognosis, and low riskof progression to AML compared with other types of MDS5q- syndrome was reported by Van den Berghe et al (1974) where by five patients were noted to have a macrocyticanaemia, normal to elevated platelet count, dyserythropoiesis, hypolobulated megakaryocytes and an interstitial deletion of the long arm of chromosome 5.[8]

Characteristics of the 5q syndrome (according to Van den Berghe, subsequently restricted to cases with marrow blasts <5% by the WHO classification3)

Clinical and Biological Features :

Female preponderance
Severe anemia
Pronounced macrocytosis
Normal or moderately decreased leucocytes
Normal or moderately increased platelets
Rare AML transformation (10%)
Prolonged survival

Bone Marrow Features

Characteristic dysmegakaryopoiesis (large monolobulated megakaryocytes with excentred nucleus)

No or moderate blast excess (restricted to marrow blasts < 5% in the WHO classification3)

Isolated 5q deletion

CONCLUSION

IGF–1 deficiency in these patientwas secondary IGF–1 deficiency caused by severe systemic illness and poor nutrition. Growth disorders of secondary sex as the effect of IGF–1 deficiency include low levels of estradiol, FSH and LH. Severe systemic illness due to congenital abnormalities includerecurrent infections of Congenital CysticAdenomatoid Malformation (CCOM) and deletion 5q Myelodisplatia syndrome (MDS).

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